EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S, and ANTON MAYR Plaintiff, v. ACAMBIS INC. and ACAMBIS PLC, Defendants.	Civil Action No. 05-614 (SLR)

DECLARATION OF LI WESTERLUND

I, Li Westerlund, Director of Intellectual Property Rights of Bavarian Nordic A/S, hereby declare:

1. I am aware that REDACTED informed that the Bavarian Vaccine Institute was closed down after the eradication of small pox in the early 1980ics.

2. Neither the Bavarian Vaccine Institute nor the state of Bavaria, or any successors or related entities, have ever contacted BN nor, upon information and belief, Professor Mayr to assert any claims of ownership to any MVA strains or any intellectual property rights.

3. As the Director of Intellectual Property Rights, I monitor world wide activities of competitors to see if they are infringing any rights of Bavarian Nordic. In that capacity, I have not encountered any unauthorized commercial uses of MVA. In particular, the commercial

marketing and sales of MVA3000 by Acambis to the U.S. Government has been the first, and only, MVA based product that has been commercially marketed and sold that we have found.

4. Upon information and belief, and as shown in various documents produced in this proceeding and its companion case at the International Trade Commission: (i) Bavarian Nordic and Acambis held a high level technical meeting in June of 2002 to discuss a licensing arrangement to develop MVA based small pox vaccines. (ii) Under terms of confidentiality, Bavarian Nordic disclosed how to make a MVA based small pox vaccine, including using MVA 572 as a starting material. (iii) After initially expressing interest, Acambis abruptly called off negotiations on terms of the arrangement, which would have called for millions of dollars to be paid to Bavarian Nordic.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Respectfully submitted,

Executed on: _____

_____

Li Westerlund, Prof., Dr., Esq.
Director of Intellectual Property Rights
Bavarian Nordic A/S
Bøgeskovvej 9
DK-3490 Kvistgård
Denmark

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S, and ANTON MAYR Plaintiff, v. ACAMBIS INC. and ACAMBIS PLC, Defendants.	Civil Action No. 05-614 (SLR)

DECLARATION OF DR. AXEL SPIES

I, Dr. Axel Spies, a German attorney (Rechtsanwalt), admitted in Düsseldorf /Germany and in good standing hereby declare:

1. I have reviewed various German Websites using search engines, such as Google.com and Google.de, yahoo.de, and search words such as " "Bavarian Vaccine Institute" and "Bayrische Landesimpfanstalt"/ "Bayerische Landesimpfanstalt " - the equivalent German terms.

2. None of my searches results indicate that a "Bayrische Landesimpfanstalt"/ "Bayerische Landesimpfanstalt " currently exists.

3. There is no listing of "Bavarian Vaccine Institute", "Bayrische Landesimpfanstalt"/ "Bayerische Landesimpfanstalt" in the German online telephone directory ("Das Telefonbuch"). Usually, vaccine or hygiene institutes are listed in Germany.

4. There is no listing of "Bavarian Vaccine Institute", Bayrische Landesimpfanstalt"/ "Bayerische Landesimpfanstalt" in the German online business (Yellow Pages) address register ("Die Gelben Seiten").

Based in these findings, I conclude that an institute under the name "Bavarian Vaccine Institute"/ "Bayrische Landesimpfanstalt"/ "Bayerische Landesimpfanstalt" does not at present exist in Germany.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Respectfully submitted,

Executed on: 01/12/07

Dr. Axel Spies, Rechtsanwalt
Bingham McCutchen LLP
2020 K Street, NW
Washington, DC 20007

EXHIBIT C

REDACTED IN ITS ENTIRETY

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S, Plaintiff, v. ACAMBIS INC. and ACAMBIS PLC, Defendants.	Civil Action No. 05-614 (SLR)

SUPPLEMENTAL EXPERT REPORT AND/OR LEGAL OPINION OF

PROF. DR. DRES. H.C. JOSEPH STRAUS

I. INTRODUCTION

1. My name is Joseph Straus and I have been retained as a legal expert on German Law by Bavarian Nordic A/S ("BN") in connection with the above-referenced case in the United States District Court for the District of Delaware to study and provide opinion on certain issues relating to ownership to and/or intellectual property rights in certain Modified Vaccinia Virus Ankara ("MVA") strains and vaccines. On October 2, 2006 I submitted my Expert Report and/or Legal Opinion.

2. After having read the Expert Report and/or Legal Opinion of Prof. Dr. Winfried Tilmann of November 10, 2006, I wish to submit the following supplementary statement.

II. EXPERT REPORT AND/OR LEGAL OPINION OF PROF. DR. WINFRIED TILMANN

3. Professor Tilmann correctly stated that for an ownership transfer, according to § 929 BGB (Bürgerliches Gesetzbuch – Civil Code), there need only be two elements: (1) change of possession and (2) agreement as to the transfer of ownership of the specific personal property transferred (No. 17).

4. Whereas no dispute exists as to the fact that in the specific samples of MVA-572 sent from Professor Mayr to Dr. Moss of the National Institutes of Health (NIH) a change in possession took place, Professor Tilmann advocates also the view that the facts of the case at issue speak for themselves that Prof. Mayr and Dr. Moss also agreed as to the transfer of ownership of the specific personal property in the respective samples. According to Professor Tilmann:

> "Prof. Mayr sent the MVA-strains to Dr. Moss/NIH at the end of August 2001 without any commentary, especially not suggesting that Dr. Moss should return them or otherwise refrain from exercising ownership over the strains. He clearly did not want these MVA-strains returned, because they were to be used by the recipient. Nor did Prof. Mayr in his letter of September 12, 2001 sent to Dr. Moss after having sent the material to him, request any return of the changed or unchanged material. He had sent these MVA-strains once and for all." (No.19).

Prof. Tilmann goes on by stating:

> "This and the acceptance of the material and the letter of September 12, 2001 by Prof. Mayr can only be understood and interpreted as establishing an agreement regarding transfer of ownership. It was neither a lease (where there is no change in ownership

because there is a duty to hand back the material), nor a service contract (no change in ownership, duty to hand back the material). Prof. Mayr gave the material and did not expect to see his "property" preserved, which would include a right on his side to call the material back. That Prof. Mayr gave up possession is given. Prof. Mayr also clearly wanted Dr. Moss/NIH to 'have and to use' the MVA-572-strains. This fulfills the necessary elements for transfer of ownership (the latter being defined in § 903 BGB as being able to do with the object what you want and to exclude others from any intrusion)." (No. 20)

5. Prof. Tilmann then interprets my Expert Report in a way as if my arguments against transfer of ownership would relate to what he calls "any underlying causal purpose-agreement." (No. 23)

6. In order to avoid any misunderstanding, I, as not disputed by Prof. Tilmann, stated that according to the so-called *Abstraktionsprinzip* both transactions (i.e. sales contract and transfer of ownership) are legally independent transactions. Moreover, I emphasized that "a provision of an MVA-572-strain for research purposes certainly does not automatically qualify as a transfer of rights for commercial purposes unless there is a specific agreement between the parties to that effect, either explicitly or based on research or industry practice." (No. 32)

7. Finally, I stated that Prof. Mayr has *neither explicitly nor implicitly agreed to transfer ownership or any commercial rights*, to Dr. Moss and/or NIH (No. 36). Thus, in my statement the transfer of ownership in MVA-572-strain has by no means been made dependent on an explicit agreement between Prof. Mayr on the one hand and Dr. Moss or NIH on the other, be it as regards the transfer of ownership, be it as regards any other "underlying agreement".

III. TRANSFER OF OWNERSHIP IN MOVABLES UNDER § 929 BGB

8. According to the case law of the German Federal Supreme Court (BGH) for the *transfer of ownership* in movables it is required that

> "the owner of the thing deliver it to the acquirer and that both agree that the ownership is transferred: It suffices, when the will for the transfer of ownership is revealed from the circumstances. Whether the will to agree exists, is to be judged according to the general principles applicable to the interpretation of legal transactions [references omitted]."[1]

9. In other words, the question, whether an agreement between the parties concerned as to the transfer of ownership is to be confirmed, depends on the circumstances of the case at issue. This, it has to be emphasized, does not relate to the underlying "causal purpose-agreement" or "any underlying obligatory purpose-agreement," in Prof. Tilmann's words, but exclusively to the *separately* and *independently* required agreement as to *the transfer of ownership*. It is also understood that the movable thing in which the ownership is to be transferred has to be specifically individualized since only in such objects a possession is possible. Therefore, ownership transfer in a quota of a larger quantity is not possible. § 929 BGB requires a separation of the specific objects.[2]

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[1] 1990 NJW 1913, left column. In the original German: "... Zur Übertragung des Eigentums an einer beweglichen Sache [ist] erforderlich, dass der Eigentümer die Sache dem Erwerber übergibt und beide darüber einig sind, dass das Eigentum übergehen soll. Es reicht aus, wenn der Wille zur Eigentumsübertragung sich aus den Umständen ergibt. Ob dieser Einigungswille vorhanden ist, beurteilt sich nach den allgemeinen Grundsätzen der Auslegung von Rechtsgeschäften" [references omitted]. Cf. also Staudinger/Wiegand, 2004, § 929 No. 9 a), with further references.

[2] Erman/Michalski, § 929 BGB No. 2, with further references to the case law of the former Reichsgericht and the BGH.

10. In the case at hand the circumstances decisive for whether an agreement *as to the transfer of ownership in MVA-572* existed in the sense of § 929 BGB cannot be reduced to the circumstances taken into account by Prof. Tilmann, i.e. to the letter of Prof. Mayr to Dr. Moss dated September 12, 2001. Rather the following circumstances count:

(i) Prof. Mayr deposited the MVA-572-strain with the European Collection of Cell Cultures (ECACC) on *January 27, 1994*, accession number 94012707. Under the rules of ECACC, the deposited strains can be accessed and released without the depositor's consent, but only for use for research purposes.

(ii) Prof. Mayr on *May 28, 1996* signed an Agreement with Bavarian Nordic, in which under No. 1.3 he offered Bavarian Nordic the *exclusive* and *sole access to MVA Vaccine Stock* and MVA Viral Stock in his possession. However, under the very same provision of that agreement it is stated:

> "Bavarian Nordic recognizes that, in the scientific community, there is a growing interest in performing basic non-commercial research including the MVA-vector. Bavarian Nordic agrees not to unreasonably use its exclusivity to the MVA-system to hinder basic research by third party non-commercial academia including the MVA-system by rejecting access to the MVA-system."

This provision is found literally in all agreements which Prof. Mayr subsequently concluded with Bavarian Nordic in June 1996, June 1999, June 2001 as well as June 2003.

(iii) With a letter dated *September 18, 1995*, Therion Biologics requested Prof. Mayr his MVA-strain of Vaccinia Virus. In the request they emphasized that "we will use this material 'for research purposes only.'" With the accompanying letter of September 26, 1995 Prof. Mayr sent to Mrs. Linda Gritz of Therion Biologics Corporation the requested material, without any further explanation.

(iv) With a letter dated *September 14, 1995*, i.e. after the MVA-572 had been deposited with ECACC, Dr. Moss, Chief of the Laboratory of Viral Diseases of NIH, wrote to Prof. Mayr:

> "As you know, my laboratory has been using the MVA-strain of Vaccinia Virus *to make recombinant expression vectors*. Until now, we have been using the virus that was brought here by Gerd Sutter. However, it would be useful to have either an official vial of seed virus used for human vaccine production or a vial of vaccine. If you could supply me with such virus including lot number and date of preparation, it would be greatly appreciated. For your convenience, you could use my Federal Express Numbers to send the material. …
>
> Thank you for considering this request."[3]

(v) With the accompanying letter of *September 19, 1995*, Prof. Mayr sent Dr. Moss the required material, without any comments.

(vi) With a letter dated *August 3, 2001* Dr. Moss again wrote to Prof. Mayr:

> "Gerd Sutter told me the good news that you have been able to locate an early sample of MVA in your freezer and have agreed to send it to me. I wish to thank you for your generosity in this regard. As you are aware, MVA has taken on a new life as the premier vaccinia virus vector. I have enclosed a reprint of a recent paper that clearly illustrates the great potential value of MVA. …
>
> Again, I thank you for your kindness in this matter."

(vii) Prof. Mayr with accompanying letter of *September 12, 2001*, without specific comments sent the requested material to Dr. Moss.

(viii) National Institutes of Health (NIH) is the largest research institution in life sciences not only in the US, but worldwide. It is a non-for profit institution.

Because of its first-class cutting edge research, Prof. Mayr sent, supported by a grant which he received from the German Public Funding Authorities, his collaborator Gerd Sutter, to NIH, primarily with the task to sequence their MVA-strain of Vaccinia Virus.

(ix) NIH has an Office of Technology Development at the National Institute of Allergy and Infectious Diseases (NIAID). According to its homepage[4]

> "The NIAID Office of Technology Development (OTD) accomplishes technology transfer by facilitating the transfer of significant research advances and resources to the broader scientific community and the development of collaborative relationships between NIAID scientists, industry, and academia. NIAID uses various mechanisms to accomplish these ends, including Material Transfer Agreements (MTAs), Co-Operative Research and Development Agreements (CRADAs), Materials-CRADAs (M-CRADas), Confidential Disclosure Agreements (CDAs), Clinical Trial Agreements (CTAs), Drug Screening Agreements (DSAs), Research Collaboration Agreements (RCAs), and, through the NIH Office of Technology Transfer (OTT), the patenting of inventions and the negotiation of various license agreements."

(x) NIAID's OTD, as the commercial exploitation arm of NIH's NIAID never on its own initiative approached Prof. Mayr, nor was it, at least not visibly, involved in any communication between Dr. Moss and Prof. Mayr.

(xi) On *January 10, 2002* Dr. Linda Gritz, Principle Scientist of Therion Biologics wrote to Prof. Mayr, *inter alia*:

> "As per our telephone conversation, I am writing to request several vials of your MVA-strain of Vaccinia Virus that were made before 1980. We

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[3] Emphasis added.

[4] http://www.3.niaid.nih.gov/about/organization/odoffices/omo/otd/about/detel/default... (last visited November 28, 2006).

are interested in testing recombinant MVA for research in human clinical trials and I am very grateful for the 1983 stocks of MVA that you sent us several years ago. However, the United States Food and Drug Administration is concerned about the possible presence of prions in cell culture material derived in Europe after 1980. Therefore we are requesting earlier (1973 or 1974 or earlier?) stocks of your MVA. We will use this material for research purposes only."

(xii) In a letter dated February 26, 2002, the same Dr. Gritz of Therion wrote to Prof. Mayr:

"As per our telephone conversation, I am writing about the MVA virus, MVA-572. CEF v. 22.2.74, that you sent to Dr. Bernard Moss. Dr. Moss is willing to send us the virus but would like *written permission from you before he sends us the virus*.

Therefore I would greatly appreciate it if you would send such a letter, giving Dr. Moss permission to provide MVA-572.CEF v. 22.2.74 (and derivatives) to Therion, at your earliest convenience: [here follow the mailing address of Dr. Moss and Dr. Gritz]."[5]

(xiii) Professor Mayr neither required nor received any compensation for the transfer of possession in MVA-572 to Dr. Moss/NIH.

11. The circumstances of the case at hand, to my understanding, do not allow any other conclusion as that there *was neither an explicit nor an implicit agreement between Prof. Mayr and Dr. Moss/NIH that the ownership in the sample of MVA-572*, i.e. the complete control to dispose of it at will, *in particular to commercially exploit*, e.g. *license or sell the progeny* of the MVA-572 strain, the *possession* of which Dr. Moss has acquired in 2001, were to

[5] Emphasis added.

be transferred to Dr. Moss and/or NIH.

12. Not only had Prof. Mayr already in 1994, i.e. before sending any MVA strains to NIH's Dr. Moss, deposited the MVA-572 virus strain with the ECACC, thus made it available for research purposes to the academic community, he also entered the contractual obligation to allow access for commercial purposes to that material to Bavarian Nordic on *an exclusive basis* in the above mentioned agreement of June 1996. Thus, assuming that Prof. Mayr agreed upon transfer of ownership in the sample sent to NIH in 2001 is clearly in contradiction with all the circumstances of the case at hand. It implies the assumption that Prof. Mayr would have on purpose treated Dr. Moss and/or NIH in a privileged way as compared to other academic researchers seeking access to MVA-572, and also that Prof. Mayr *knowingly* violated his contractual obligations with Bavarian Nordic. Moreover, such an assumption is also *clearly inconsistent with the denial of Dr. Moss* to send samples of MVA-572 virus to Therion Biologics without *written permission* of Prof. Mayr.

13. The *ex post* attempts of NIAID and its OTD, which first requested Dr. Moss not to reply to complaints raised by Prof. Mayr (see letter of Dr. Moss of April 23, 2003), to claim that NIH acquired, *free of any charge and any payment of any consideration and without any MTA* all rights with respect to the material, progeny and derivatives of the MVA-572.FHE-22.02.1974 that Prof. Mayr supplied to Dr. Bernard Moss in late summer 2001 (letter of Dr. John R. La Montagne of December 10, 2002), *find no support in the circumstances of the case.* Prof. Mayr had no reason to treat Dr. Moss and/or NIH as a non-for profit research institution any differently than any other colleague, who approached him with a request to access his MVA viral strains. There should be no doubt, especially in view of the circumstances described, that Prof. Mayr for sure would have acted differently if NIAID's OTD would have been involved in

the transfer of the respective strains on the side of Dr. Moss and NIH.

14. Without going into details, it should be added that the assessment of the alleged ownership in MVA-572.FHE-22.02.1974, by NIH's NIAID itself seems to be reflected in the MTA signed between NIAID and Acambis, Inc., in 2002, where as regards that material, No. 10 reads as follows:

> "NO WARRANTIES, EXPRESSED OR IMPLIED, ARE OFFERED AS TO THE MERCHANTABILITY OR FITNESS FOR ANY PURPOSE OF THE MATERIALS PROVIDED TO RECIPIENT UNDER THIS AGREEMENT, OR THAT THE MATERIALS OR COMMERCIAL PRODUCTS MAY BE EXPLOITED WITHOUT INFRINGING THE PATENT RIGHTS OF ANY PARTIES. Recipient accepts transfer of the material "as is", and NIAID does not offer any guarantee of any kind."[6]

15. For the sake of completeness only, it should finally be observed that in view of the specific properties of the material at hand, namely *its ability to be reproduced in a biological system*, thus, its use, even for research purposes only, being dependent on continuous reproduction of the strain, all comparisons of any acts typical of ownership in movables, *which are not biological material*, are vastly misplaced and, as a rule, not suitable to contribute to an adequate understanding of the issues at hand. This relates in particular to acts such as destruction, return of the material, etc. Not surprisingly, many distributors of biological materials, who for instance use the so-called lease-license model, do not even require or expect the return of the physical materials. The recipient may destroy the materials or retain them

[6] Emphasis in the original.

indefinitely. But restrictions apply to further transfers by the recipient.[7] Thus, the fact alone that a recipient of biological material may destroy it or retain it indefinitely, does not bear any significance as to the ownership in such material.

IV. CONCLUSION

16. Under the case law of the German Federal Supreme Court (BGH) in the case at hand, as a consequence of the *clear lack of a respective agreement*, no transfer of ownership from Prof. Mayr to NIH/Dr. Moss in MVA-572 has taken place under § 929 BGB. This lack of agreement as to the transfer of ownership ("Einigungswille") relates exclusively and specifically to the so-called "Verfügungsgeschäft", i.e. the transfer of ownership *in abstracto*.

Munich, November 29, 2006

Prof. Dr. Dres. h.c. Joseph Straus

[7] O'Connor, The Use of MTAs to Control Commercialization of Stem Cell Diagnostics and Therapeutics, Berkeley Technology Law Journal Vol. 21:3, 1017 ss., at 1019, 1020 [2006].

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on this 29th day of November 2006, copies of BAVARIAN NORDIC'S SUPPLEMENTAL EXPERT REPORT AND/OR LEGAL OPINION OF PROF. DR. DRES. H.C. STRAUS were served as follows:

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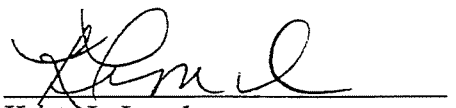

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EXHIBITS E AND F

REDACTED IN THEIR ENTIRETY

EXHIBIT G

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAVARIAN NORDIC A/S, Plaintiff, v. ACAMBIS INC. and ACAMBIS PLC, Defendants.	Civil Action No. 05-614 (SLR)

SECOND SUPPLEMENTARY EXPERT REPORT AND/OR LEGAL OPINION OF

PROF. DR. DRES. H.C. JOSEPH STRAUS

In addition to the opinions and testimony, I expressed in my prior statements, I am likely to testify as follows:

1. I recently met with Professor Anton Mayr, in order to confirm my understanding of how, when and where he created various MVA strains, including MVA 572 strain. I did this because I understood that Prof. Mayr is elderly and has given testimony in depositions in the last twelve months which has been used by counsel for Acambis to argue that Prof. Mayr did not own the MVA 572 strain.

2. Prof. Mayr's comments made during the recent meeting support the opinions and facts stated in my prior statements, submitted in this case. Thus, I have relied on my discussion with Prof. Mayr in forming the opinions I hold in this proceeding. This was also the reason why I did not view it necessary to mention my meeting with Prof. Mayr in my Supplementary Statement of November 30, 2006.

3. During my recent deposition, I was shown a document purported to be an English translation of a Swiss patent indicating Professor Dr. Anton Helmut Stickl as inventor and the Free State of Bavaria as owner. I was asked if this did not in fact indicate that Prof. Stickl or the Free State of Bavaria were somehow owners of MVA 572 strains.

4. Through my own investigations, I was able to discover the published German application (Offenlegungsschrift) on which the priority claim (September 11, 1971 – 2145477) of the Swiss patent was based. Thereby I found the following: Whereas in the Swiss patent only Prof. Stickl is named as inventor, the German Offenlegungsschrift 2145477 reveals that in the original filing of September 11, 1971, only Prof. Stickl was named as inventor. Two years later (Correction Nr. L.37/73), however, Prof. Mayr's name was added. Moreover, whereas the claims of the Swiss patent relate to a process for culturing a virus intended for producing an inoculant against smallpox, the later submitted new claims in the German patent document relate to a vaccine for intracutein smallpox vaccination, characterized in that the vaccine is composed of attenuated, modified vaccinia viruses (Claim 1), or (dependent Claim 2) characterized in that the vaccine is generated through the use of vaccinia-Ankara virus, which has been bred over 500 passages in chicken fibroblast cells.

5. Although the entire file of the German Patent Office related to the file number P 21 45 477 is not available any more (seemingly only the published documents and the file history still exist) the discrepancies between the Swiss and the German patent document indicate to my understanding that Prof. Stickl without knowledge of Prof. Mayr filed the applications, first in Germany, in 1971, and subsequently in Switzerland, in September 1972. Since Prof. Mayr clearly must have been the inventor of the respective strains, his name was added in the

German application, but seemingly not in the Swiss one, if the document shown to me correctly reproduces the complete Swiss documents.

6. I would also like to emphasize that according to the German Offenlegungsschrift the title of the respective invention was "Verfahren zur Pockenschutzimpfung" ("Method for Smallpox Vaccination"). This indicates that originally Prof. Stickl applied for a method patent for vaccination and not for a product patent related to strain(s). This would explain my understanding of the role of Prof. Stickl cooperating with Prof. Mayr, namely primarily performing tests with MVA strains produced and owned by Prof. Mayr.

7. Finally, it should be added that neither the German patent document, nor the Swiss document relate to any specifically identified MVA strain, especially not to MVA 572. Thus, apart from the fact that I am convinced, based on the facts which I have learned in the course of these proceedings, that only Prof. Mayr could have been the inventor and the owner of the respective MVA 572 strain, the two patent documents had no bearing as to the tangible ownership of any MVA strain.

8. I have appended to my current statement the German Offenlegungsschrift as it can be downloaded from the Internet. In addition to that also the history of the file as summarized in the official document of the German Patent Office as downloaded, on December 1, 2006, is also appended.

Prof. Dr. Dres. h.c. Joseph Straus

December 6, 2006

(51) Int. Cl.: A 61 k, 23/00

BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(52) Deutsche Kl.: 30 h, 6

(10) Offenlegungsschrift 2145477

(11) Aktenzeichen: P 21 45 477.3
(21) Anmeldetag: 11. September 1971
(22) Offenlegungstag: 15. März 1973
(43)

Ausstellungspriorität: —

(32) Unionspriorität
(22) Datum: —
(33) Land: —
(31) Aktenzeichen: —

(54) Bezeichnung: Verfahren zur Pockenschutzimpfung

(61) Zusatz zu: —
(62) Ausscheidung aus: —

(71) Anmelder: Freistaat Bayern, vertreten durch Bayer. Staatsministerium des Innern, 8000 München

Vertreter gem. § 16 PatG: —

(72) Als Erfinder benannt: Stickl, Helmut, Prof. Dr. med., 8033 Krailling
Mayr, Anton, Prof. Dr. 8000 München

rgl. Ber.-L. 37/73

DT 2145477

Freistaat Bayern vertreten durch
Bayer. Staatsministerium des Innern
8 München 22, Odeonsplatz 3

2145477

Verfahren zur Pockenschutzimpfung

Die Erfindung betrifft ein Verfahren zur Pockenschutzimpfung.

Bei der bisher üblichen Impfung gegen Pocken unter Verwendung eines stark reaktogenen Impfstammes und unter Anwendung der epicutanen Skarifikation bei Insertion des Virus kommt es in bestimmtem zeitlichem Ablauf zur Ausbildung einer Impfpustel. Letztere ist Ausdruck eines infektiös-allergischen Geschehens, wobei zellulär-allergische Reaktionen im Vordergrund stehen.

Es ist eine schon seit längerer Zeit bekannte Tatsache, daß die Reaktogenität einer Impfung nicht identisch ist mit deren Immunogenität; dies bedeutet, daß starke Impfreaktionen nicht auch zu einem starken Infektionsschutz gegenüber dem krankmachenden Variola-Virus führen müssen. Diese Erkenntnis war in den letzten Jahren Grund für die Einführung des weniger reaktogenen Impfstammes Elstree, allerdings auch unter Anwendung der epicutanen Skarifikation.

Der Nachteil dieser Art der Pockenschutzimpfung besteht darin, daß sie in nicht seltenen Fällen, besonders wenn es zu einer zusätzlichen Sensibilisierung gekommen ist, zu EEG-Veränderungen führt. Ursache hierfür sind phylogenetisch angelegte funktionelle Brücken zwischen Zentralnervensystem und Haut.

Aus diesem Grunde erscheinen die Forderungen, bei der Pockenimpfung eine cutane Pustelreaktion herbeizuführen und gleichzeitig eine risikofreie Impfung durchführen zu wollen, miteinander nicht vereinbar; denn so lange eine

so ausgeprägte immun-allergische Reaktion an der Haut erzwungen wird, kann nicht verhindert werden, daß nicht auch neuroallergische Begleitreaktionen am Zentralnervensystem auftreten.

Man hat daher versucht, mit sogenannten "Attenuierten Impfstoffen" zu arbeiten. Alle diese Versuche gingen davon aus, daß normales Vaccinia-Virus über 20 bis 50 Passagen auf der Chorion-allantoismembran gezüchtet wurde und dann in einer relativ hohen Konzentration bei der Impfung zur Anwendung kam. Die Passage des Impfvirus über den Hühner-Embryo führte in der Tat zu einer Selektion nicht einheitlicher Impfstämme, so daß nach mehreren Kulturen ein genetisch im wesentlichen einheitlicher Impfstamm gewonnen werden konnte. Ferner kam es bei diesen Impfstoffen zu einem Rückgang der Reaktogenität, d.h., daß die lokale Impfreaktion milder war und weniger Impffieber auftrat; auch die Virämierate bei Impfung mit solchen Impfstoffen ist deutlich reduziert. Aber auch bei dieser Methode wurde nicht auf die pustulöse Impfreaktion verzichtet. Dementsprechend waren bei Impfungen mit diesen Impfstämmen ebenfalls zentral-nervöse Komplikationen mit fast der gleichen Erwartungsfrequenz wie nach Impfung mit konventionellen Impfstoffen eingetreten.

Schließlich hat man auch schon versucht, mit normalem Impfstoff entweder subcutan zu impfen - das ergab bis zu 60 % Schwellungen im Unterhautgewebe -, oder aber intracutan - das ergab ebenfalls wieder Pusteln und zwar mit Gewebenekrosen.

Demgegenüber geht die Erfindung von der Erkenntnis aus, daß es - um die Nachteile aller bisher bekannten Pockenschutzimpfverfahren zu vermeiden - darauf ankommt, einen Impfstoff zu verwenden, bei dem keine cutane Impfreaktion wie Bildung einer Impfpustel auftritt.

Gemäß der Erfindung wird dies durch ein Verfahren zur Pockenschutzimpfung erreicht, bei dem intracutan mit attenuiertem, modifiziertem Impfstoff geimpft wird. Vorteilhafterweise wird dazu das Vaccinia-Virus Ankara verwendet, das in über 500 Passagen in Hühner-Fibroblasten-Zellen gezüchtet ist, so daß ein modifiziertes, genetisch einheitliches, in seiner Reaktogenität und Virulenz durch die Zellpassagen abgeschwächtes Vaccinia-Virus vorliegt. Dabei enthalten 1 ccm des Fertigimpfstoffes, in gereinigter lyophilisierter Form, etwa 10^7 Viruspartikel; 0,1 ccm bis maximal 0,2 ccm werden intracutan injiziert. Damit ist eine genauere Dosierung als bei den bisher bekannten Impfverfahren möglich. Außerdem ist aber eine Kontrolle des Impfverlaufes dadurch gegeben, daß sich an Ort und Stelle der Injektion Rötung, leichte Schwellung mit Durchmesser von 4 x 8 mm und manchmal auch Juckreiz zeigen; es kommt aber auf keinen Fall zu einer pustulösen Impfreaktion. Eine humorale (serumgebundene) und gewebliche Sensibilisierung (Allergie) in klinisch nennenswerter Form tritt also nicht ein, jedoch ist eine cellulläre Immunität, die eine Ausbreitung und Vermehrung im Gewebe verhindert, nachweisbar.

Bei Anwendung des erfindungsgemäßen Verfahrens läuft die Impfreaktion ohne Fieber und beeinträchtigende andere Allgemeinerscheinungen ab, im Gegensatz zu den bisher bekannten Impfverfahren, bei denen zuweilen Krankheitserscheinungen wie Impffieber, Impf-Ulcus (Geschwür), Impf-Exanthem (Ausschlag) auftreten und sogar Gehirnzellen-Entzündung, die stets zu bleibenden Schäden, wenn nicht zum Tode führt.

Nach Ablauf von 8 Tagen nach der Injektion bilden sich Rötung und Schwellung zurück, es bleibt dann aber zunächst am Ort der Injektion noch ein kleines gelblich-bräunliches Knötchen zu sehen und zu tasten, das jedoch spätestens nach 21 Tagen vollständig verschwindet.

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Ein weiterer wesentlicher Vorteil des erfindungsgemäßen Verfahrens ist darin zu sehen, daß durch seine Anwendung eine vaccinale Basisimmunität geschaffen werden kann, die verhindert, an den vorgenannten Komplikationen der bekannten Impfverfahren zu erkranken. Wenn diese Basisimmunität vorhanden ist, dann können alle weiteren Pockenschutzimpfungen nach den üblichen Verfahren nicht mehr zur Gehirnzellenentzündung führen. Das erfindungsgemäße Verfahren ist daher geeignet, die Impfung bei bisher durch Alter oder Krankheit bedingten unumgänglichen Impfhindernissen gefahrlos durchzuführen.

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Anlage

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Neue Patentansprüche
zur Anmeldung P 21 45 477.3

1. Impfstoff für die intracutane Pockenschutzimpfung,

dadurch gekennzeichnet,
daß der Impfstoff aus attenuierten, modifizierten Vaccinia-Viren besteht.

2. Impfstoff nach Patentanspruch 1,

dadurch gekennzeichnet,
daß der Impfstoff durch Verwendung des Vaccinia-Virus Ankara gebildet ist, das in über 500 Passagen in Hühner-Fibroblasten-Zellen gezüchtet ist.

DPINFO

DPMA **Deutsches Patent- und Markenamt**

Patent- und Gebrauchsmusterregister

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11.09.71 Anmeldetag
Die Anmeldung ist nicht anhängig/das Schutzrecht ist erloschen
Letzter Stand des Verfahrens:
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Erfassungsdatum: 01.07.1985

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Patent- und Gebrauchsmusterregister

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UG55 - Vertreter:

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UG58 - Erfinder:

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CERTIFICATE OF SERVICE

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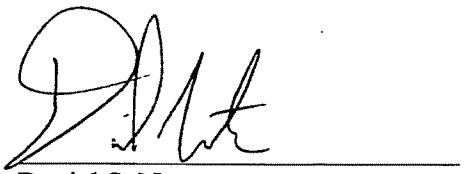

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EXHIBITS H AND I

REDACTED IN THEIR ENTIRETY